REMARKS

Favorable reconsideration and allowance of the present application are respectfully requested in view of the following remarks.

Claims 1-6, 9-13, and 39-45 are pending in the present application including independent claim 1. In the Office Action, independent claim 1 was rejected under *35 U.S.C. § 103(a)* as being obvious over Rylatt, et al. (International Application Publication No. WO 97/09620) as evidenced by Fitzpatrick, et al. (U.S. Patent No. 6,121,008) in view of Virtanen (U.S. Patent Application Publication No. 2005/0214827) and Jou, et al. (U.S. Patent No. 5,670,381).

Rylatt, et al. is directed to a method that involves the use of a test zone containing an analyte receptor capable of binding to the target analyte and a calibration zone containing a calibration agent receptor capable of binding a calibration agent. The signals associated with the labels at the test zone and calibration zone are measured to determine the target analyte in the test sample. In Example 1 and Fig. 2, for instance, a device is shown for detecting the analyte D-dimer. The device includes a test zone 204 containing an analyte receptor 215 (i.e., monoclonal antibody DD-1D2/48 1D2 antibody) that binds to D-dimer when complexed to an analyte detection agent 208 (i.e., D-dimer binding monoclonal antibody DD-3B6/22 labeled with colloidal gold). The device also includes two calibration zones 210, 211 containing BSA labeled with biotin 214, 216 for binding to the calibration agent 209 (i.e., streptavidin labeled with colloidal gold). Further, the device includes a procedural control zone 212 containing an anti-mouse antibody 217 capable of specifically binding the analyte detection agent 208.

Rylatt, et al. fails to disclose various aspects of independent claim 1. For instance, as correctly noted by the Examiner, Rylatt, et al. fails to disclose the use of a polyelectrolyte having a net charge opposite to that of the conjugated detection probes.

In addition, Rylatt, et al. fails to disclose a device in which the amount of the analyte within the test sample is proportional to the ratio of said detection signal intensity to said compensation signal intensity, as calibrated by said calibration signal intensity. In fact, Rylatt, et al. specifically states that "comparison of the signals generated in at least one test zone and the at least one calibration zone is used to determine the approximate concentration of the analyte in the test sample" (p. 12, ll. 8-10). The signal of the procedural control zone of Rylatt, et al. is not incorporated in determining the concentration of an analyte in a test sample.

As explained in the present application and previous responses, the signal from the compensation zone of the captioned application can compensate for the lost signal resulting from those probes that are embedded too deep within the interior of the assay device and/or those probes that exhibit self-quenching. In this regard, independent claim 1 requires that the *amount of the analyte within the test sample is proportional to the ratio of the detection signal intensity to the compensation signal intensity*, as calibrated by the calibration signal intensity. Rylatt, et al. does not disclose or suggest this claim limitation.

Nevertheless, the Office Action combined Rylatt, et al. with Virtanen and Jou, et al. in an attempt to render obvious independent claim 1.

Devices of Virtanen utilize patterned deposition of multiple signal elements on a single supporting member or substrate to detect the presence of an analyte in a sample.

Specifically, according to Virtanen, a substrate is provided with a derivatized surface to which is attached cleavable spacer molecules including cleavage site. Each of the cleavable spacer molecules is attached at one end to the substrate surface and at the other end to a signal generating means, which can be a metal particle, colloidal metal or nonmetal labels, dyed plastic particles or similar materials (col. 28, l. 23 – col. 29, l. 12). Analyte specificity is conferred upon the cleavable spacer by side members. Upon application of a test solution containing antigen to the device, antigen binds the side members, preventing decoupling of the signal generating means when the cleavage site is cleaved by contact with a chemical cleaving agent. (Col. 11, l. 58 – col. 14, l. 38.) During use, a fluid sample is applied to the assay device and distributed over the substrate. After an appropriate incubation period, a wash step may be performed. Following, a solution including a cleaving agent is added and distributed over the surface of the disk. (Col. 15, l. 34 – col. 16, l. 63.) After rinsing and removal of the cleaved reflective signal moieties that are not protected by the specific binding of analyte, the disk may be read directly (col. 18, ll. 50-53).

As correctly noted in the Office Action, the signal generating means (e.g., metal spheres) of Virtanen may be coated with detergents or derivatized so that they will have a surface charge and thus be prevented from attaching nonspecifically with surfaces. Accordingly, particles that are not fixed by the presence of the analyte are rinsed from the device, while particles that are fixed by the analyte will remain on the device.

Jou, et al. discloses a sandwich assay including a soluble capture reagent formed by an analyte-specific binding member that has been bound to a charged substance. In solution, the capture reagent is contacted with a test sample suspected

of containing an analyte and is also contacted with an indicator reagent. The indicator reagent includes a specific binding member and a detectable label. Upon one- or two-step mixing, a binding reaction results in the formation of a capture reagent/analyte/indicator reagent complex. This complex is in solution and still in the reaction mixture. The assay also includes the step of separation of the complex from the reaction mixture by using a solid phase that is either oppositely charged with respect to the charged substance of the capture reagent or that retains a second oppositely charged substance. (Col. 22, ll. 29-62.) The assay can be performed in a porous solid phase material (col. 24, ll. 52-54). The porous material can include a reaction zone containing the second charged substance such that the capture reagent and complexes thereof are immobilized in the reaction zone by the interaction of the two oppositely charged substances (col. 6, ll. 32-37).

The charged substances of Jou, et al. are used to enhance the immobilization of the complexes on the solid phase (e.g., porous material). Thus, the charged substance of Jou, et al. binds the capture reagent that includes an analyte-specific binding member and a charged substance. When analyte is present, a complex is formed between the capture reagent, the analyte, and the indicator reagent, and binding between the charged substance and the capture reagent leads to the indirect binding of the indicator reagent and detection of the analyte bound between the two. When analyte is not present, the capture reagent will still bind the charged substance, but because no analyte is present to form the sandwich, no indicator reagent will be bound. Accordingly, the charged substance of Jou, et al. nonspecifically binds either uncomplexed capture reagent or capture reagent that is complexed with both analyte

and an indicator reagent. The charged substance does not, however bind uncomplexed indicator reagent. The only time that indicator reagent is bound in Jou, et al. is when it is complexed to an analyte and a capture reagent.

In order to combine the references as suggested to arrive at captioned claim 1, one of ordinary skill in the art would need to completely restructure the device of Rylatt, et al. Initially, one would need to alter the label of Rylatt, et al. through coating or derivatizing so that the label will have a surface charge as disclosed by Virtanen. Following this first alteration, one would need to further alter the device and substitute the specifically binding antibody of the procedural control zone of Rylatt, et al. with a charged substance as is found in Jou, et al. One would then need to utilize this charged substance to nonspecifically bind both complexed and uncomplexed analyte detection agent, which now contain a surface charge on the detectable labels. Finally, one would need to incorporate the signal from this altered procedural control zone in determining the amount of the analyte in a test sample.

Applicants respectfully submit, however, that the references either teach away from or fail to disclose these suggested modifications. For instance, as correctly noted in the Office Action, Virtanen teaches the addition of a surface charge to a particle for the purpose of preventing nonspecific binding of the particle to a surface. Thus, the particles of Virtanen, once mobilized, *will not* bind to a substrate. However, this teaching completely contradicts the suggested modification of Rylatt, et al. in which surface charged particles *will* nonspecifically bind to the substrate at the procedural zone. One of ordinary skill in the art, upon reading Virtanen, would be led in a direction completely opposite of that suggested by the Office Action. In order to arrive at the

present invention, one of skill in the art would require teaching that *encourages* the nonspecific binding of the mobilized labels at the procedural control zone, but Virtanen *discourages* the nonspecific binding of mobile, surface charged labels on a surface.

Jou, et al. also teaches against the suggested combination. According to Jou, et al. a nonspecific charged substance binds both uncomplexed capture reagent and complexed capture reagent in a zone of the device. Thus, when analyte is present, the indicator reagent will be bound in the zone and a positive result is evident. If the analyte is present in a small amount, such that excessive uncomplexed capture reagent is bound in the zone along with the complexed capture reagent, the test device will still function accurately, as the only indicator reagent bound in the zone is complexed to the analyte, and a positive test result is still provided. As correctly noted in the Office Action, this increases the potential number of complexes that can be immobilized on the solid support and moreover, does so in a way that still provides an accurate result. According to the suggested modification however, rather than utilizing a charged substance to nonspecifically bind both complexed and noncomplexed capture reagent in a zone, a charged substance would be utilized to bind both complexed and uncomplexed indicator reagent in a zone.

Jou, et al. teaches against such a modification as the modification would destroy the function of the reference. If one were to nonspecifically bind both uncomplexed and complexed indicator reagent in the zone of Jou, et al., it would no longer be possible to tell the difference between a positive result when the indicator reagent is complexed and a negative result, when the indicator is uncomplexed, as the indicator reagent would be bound in both cases. One of ordinary skill in the art, upon reading Jou, et al.

would be led down a path in which both uncomplexed and complexed capture reagent can be nonspecifically bound in a single zone by use of a charged substance in the zone. In order to arrive at the present invention, one of skill in the art would require teaching directed toward nonspecific binding of both complexed and uncomplexed *indicator reagent* in a single zone, but Jou, et al. teaches nonspecific binding of both complexed and uncomplexed *capture reagent* at a single zone. Moreover, the device of Jou, et al. would not function under the suggested modified conditions. Accordingly, Applicants respectfully submit that Jou, et al. teaches away from the suggested modification.

Finally, none of the references disclose or suggest a device in which the amount of the analyte within the test sample is proportional to the ratio of a detection signal intensity to a compensation signal intensity, as calibrated by a calibration signal intensity, as is found in claim 1.

For at least the reasons indicated above, Applicants respectfully submit that the present claims patentably define over the cited references, taken singularly or in any proper combination. Applicants emphasize that an invention is not obvious simply because various parts of the claims may be found somewhere in the prior art. If this were the case, virtually every invention would be considered obvious. Instead, the proper standard under *§ 103* is whether the claimed invention *as a whole* when viewing the teachings of the references *in their entirety*. In this case, as explained above, the present claims are so substantially different from the references, when properly viewed in their entirety, that one of ordinary skill in the art would not have conceivably modified and/or combined the references as suggested in the Office Action.

It is believed that the present application is in complete condition for allowance and favorable action, therefore, is respectfully requested. Examiner DiRamio is invited and encouraged to telephone the undersigned, however, should any issues remain after consideration of this Response.

Please charge any additional fees required by this Response to Deposit Account No. 04-1403.

Respectfully requested,

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7/31/09
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